March 7, 2005

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398
Tel. 919 483 2100
www.gsk.com

Management Dockets, N/A
Dockets Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: NAS 0; Not Product Specific
Response to FDA Request/Comment: ICH Draft Guidance on S8 Immunotoxicity Studies for Human Pharmaceuticals
[Docket No. 2005D - 0021]

Dear Sir or Madam:

Enclosed please find comments from GlaxoSmithKline on the 'International Conference on Harmonisation; Draft Guidance on S8 Immunotoxicity Studies for Human Pharmaceuticals'. We would like to thank the ICH Steering Committee for the opportunity for comment on the ICH Harmonised Tripartite Guideline draft document. Members of the Immunologic Toxicology Department and Safety Assessment in GSK have reviewed the Guideline document, and in general, welcome the approach taken by ICH. However, there are several statements within the document where GSK would like to offer recommendations for consideration. Specific comments are provided on subsequent pages, organized under the same section headings as used in the draft guidance and cross-referenced by line number.

This submission is provided in electronic format according to the instructions provided at http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm?AGENCY=FDA.

Please contact me at (919) 483-6405 or my colleague Derek Newall, at (44 011) 192-088-3356, if you require clarification or have questions about these comments. Thank you.

Sincerely,

Anne N. Stokley, M.S.P.H.
Director, Policy, Intelligence & Education
US Regulatory Affairs

GlaxoSmithKline Comments on ICH Draft Guidance on S8 Immunotoxicity Studies for Human Pharmaceuticals

1. INTRODUCTION

It is recommended that following the sentence on Lines 69-71: *"Much of the science and method development and validation efforts in the past have been focused on evaluating drug development candidates for their potential to be either immunosuppressive or contact (dermal) sensitizers."*, an additional sentence will be included: "*The term immunotoxicity in this guideline will primarily refer to immunosuppression, i.e. a state of increased susceptibility to infections or the development of tumors.*" We feel this change will increase clarity and focus of the guideline.

1.3. Scope of the Guideline

It is recommended to delete sentence on Lines 109-111: "*The term immunotoxicity in this guideline will primarily refer to immunosuppression, i.e. a state of increased susceptibility to infections or the development of tumors.*" As recommended above, this sentence has been moved from the Scope of the Guideline to the Introduction.

2.1.1 Standard toxicity studies

"(3) Decreased basal serum immunoglobulins – serum globulins are a rather insensitive marker of immunotoxicity due to the long half life of immunoglobulins. However, changes in globulins that occur without a plausible explanation can indicate potential immunotoxicity."
It is recommended to replace *"immunoglobulins*" from Line 153 by the term "*globulins*" to consistently use terminology in this paragraph.

In addition, we suggest to expand this paragraph by addressing additional factors influencing the measurement of serum globulins, e.g., *quantification of total globulins includes many plasma proteins other than immunoglobulins, and it can be affected by suppression of hepatic protein synthesis and/or protein loosing intestinal or renal consequences. So measurement of globulins is not a specific indicator of immune status, but can be helpful when taken along with macroscopic and histological assessment of immunofunctional organs and hematological profiles.*

It is recommended to replace text in the bullet on Line 165
from:

- "*statistical and biological significance of the changes,* "

to:

- "*biological indicators and/or statistical significance of the changes,*"

We feel that biological indicators of changes should carry more weight in the data interpretation than the statistical significance.

2.1.2 Other Causes for Concern in the Weight-of-Evidence Review

Text on Lines 197-198 needs further clarification:
"(3) Compounds structurally similar to compounds with known immunosuppressive properties should also be considered for additional immunotoxicity testing."

The used term "*structurally similar*" is insufficiently defined to be understood by all parties and without objective definition of "similar" the guidance will be inconsistently followed.

Appendix 1

Methods to Evaluate Immunotoxicity
1.2 Gross Pathology and Organ Weights

It is recommended to delete word "All" from the sentence on Line 293:
"*All lymphoid tissues should be evaluated for gross changes at necropsy.*"

Based on our experience evaluation of "all" lymphoid tissues is not practical on current regulatory toxicology studies.

2.2 T-cell Dependent Antibody Response (TDAR)

It is recommended to modify text on Lines 358-360
from:
"*Antibody can be measured by using an ELISA or other immunoassay methods. One advantage of this method over the antibody forming cell response is that samples can be collected serially during the study.*"
to:
"Antibody can be measured by using an ELISA or other immunoassay methods. One advantage of this method over the antibody forming cell response is that samples can be collected serially during the study and both IgM and IgG antibodies can be evaluated."

This change will be consistent with recently published data indicating that primary antibodies of IgG class may be more sensitive endpoint than IgM.

2.3 Immunophenotyping

It is recommended to delete sentence on Lines 391-392:
"However, flow cytometry can be used to measure antigen-specific immune responses of lymphocytes."

We feel there is no sufficient information indicating that this evaluation can be conducted. Otherwise, some clarification and a reference should be added in support of this statement.

2.5 Host Resistance Studies

It is recommended to modify text on Lines 409-415
from:
"*Host resistance studies involve challenging groups of mice or rats treated with the different doses of test compound with varying concentrations of a pathogen (bacteria, viral, parasitic) or tumor cells. Infectivity of the pathogens or tumor burden observed in vehicle versus test compound treated animals is used to determine if the test compound is able to alter host resistance. Models have been developed to evaluate a wide range of pathogens such as Listeria monocytogenes, Streptoccous pneumoniae, influenza virus, cytomegalovirus, Plasmodium yoelii and Trichinella spiralis.*"
to:
"*Host resistance studies involve challenging groups of mice or rats treated with the different doses of test compound with varying concentrations of a pathogen (bacterial, fungal, viral, parasitic) or tumor cells. Infectivity of the pathogens or tumor burden observed in vehicle versus test compound treated animals is used to determine if the test compound is able to alter host resistance. Models have been developed to evaluate a wide range of pathogens such as Listeria monocytogenes, Streptoccous pneumoniae, Candida albicans, influenza virus, cytomegalovirus, Plasmodium yoelii and Trichinella spiralis.*"

This change will be consistent with the use of fungal (*C. albicans*) model for host resistance studies that has been established and published in literature.